REMARKS

Claims 95 and 100-126 are pending. Claims 100, 106-107, 109-110, 112, 114 and 115 are amended. The amendments are supported by the application as filed, thus there is no issue of new matter. Claims 95, 101-105, 108, 111 and 126 are cancelled without disclaimer or prejudice to applicants' right to pursue patent protection for the subject matter of these claims in another application. Claims 100, 106, 107, 109, 110 and 112-125 thus appear in the application. Entry of this Amendment is respectfully requested since it is believed to place the application in condition for allowance, or at a minimum to materially reduce the issues for an appeal.

Support for the claim amendments is found, *inter alia*, in the specification as follows: **Claim 100**: page 12, lines 15-16, page 13, lines 8-10, page 14, lines 1-5 and page 53, line 35 to page 54, line 4; **Claims 106-107**: page 13, lines 8-10 and dependencies changed from claim 102 to 100 due to the cancellation of claim 102; **Claims 109-110**: dependencies changed from claim 108 to 100 due to the cancellation of claim 108; **Claim 112**: page 13, lines 8-10; **Claim 114**: page 12, lines 15-16, page 13, lines 8-10, page 14, lines 1-5 and page 53, line 35 to page 54, line 4; **Claim 115**: page 12, lines 15-16, page 13, lines 8-10, page 14, lines 1-5, page 15, line 27 to page 16, line 5, page 53, line 35 to page 54, line 4 and the Experimental Results discussed at pages 36-118.

Applicants note their appreciation for the courtesies extended by Examiner Holleran and her Supervisor, Examiner Anthony Caputa, to their representatives, John P. White, Esq. and Mark A. Farley, Esq. during a telephone interview concerning related application Serial No. 08/196,154 on Tuesday, December 2, 2003. The amendments and comments submitted in this Response are in accordance with the matters discussed during that telephone

interview and thus constitute a written record thereof.

REJECTIONS WITHDRAWN

In ¶4 of the Office Action The Examiner stated that the provisional double-patenting rejection of claims 78, 80-92 and 94-99 (and new claims 100-126) over Application No. 08/475,784 is withdrawn because the claims of the instant application are directed to conjugates comprising a GM2 or GD2 ganglioside, whereas the claims of 08/475,784 are directed to conjugates comprising GD3 gangliosides.

OBJECTIONS/REJECTIONS MAINTAINED

The Examiner stated in ¶5 on pages 2-3 of the Office Action that the prior objection to the disclosure is maintained for the reasons set forth in the Office Action mailed 6/10/96 (Paper No. 9). The Examiner stated that Applicants submit they will provide a new Figure 6B to overcome the rejection when the case is in condition for allowance, but that until applicants submit a proper Figure, the objection is maintained.

In Paper No. 9, the Examiner stated that on page 5, line 30 of the application, in the Brief Description of the Figures, Figure 6b is listed as IgG antibodies but Figure 6b has the y-axis labeled as IgM titer. The Examiner thus stated that the appropriate correction is required.

Attached hereto as **Exhibit A** is an annotated (marked-up) copy of Figure 6B indicating in red ink a proposed change wherein the Y-axis is now labeled as "IgG". **Exhibit B** is a replacement drawing sheet with the above-identified change made to the labeling of the Y-axis. The amendment to Figure 6B is supported by page 5 of applicants' specification. Applicants respectfully request entry of this drawing correction as it raises no issue of new matter. The Examiner is

requested to reconsider and withdraw the objection to the disclosure in view of the submission of the corrected Figure.

Double-Patenting Rejections

In ¶6 of the Office Action the Examiner stated that the provisional double-patenting rejection of claims 100-126 over Application No. 08/477,147 is maintained for the reasons of record. The Examiner stated that Applicants argue that the claims of 08/477,147 do not render obvious the instant claims and that Applicants' arguments have been fully considered but are not persuasive because Applicants have provided no reasoning to dispute the obviousness set forth in previous Office Actions.

In ¶7 of the Office Action the Examiner stated that claims 100-126 are provisionally rejected for obviousness-type double patenting over claims 119-143 of copending Application No. 08/196,154 for the reasons of record. The Examiner stated that Applicants argue that the claims of 08/196,154 do not render obvious the instant claims and that Applicants' arguments have been fully considered but they are not persuasive, because Applicants have provided no reasoning to dispute the obviousness set forth in previous Office Actions.

In response to these provisional double-patenting rejections, submit herewith as **Exhibit C** is a Terminal Disclaimer over any patent issued from U.S. Serial No. 08/477,147 and any patent issued from U.S. Serial No. 08/196,154. The disclaimer has been executed by an authorized representative of Sloan-Kettering Institute For Cancer Research, i.e., the Assignee of the present application as well as of U.S. Serial Nos. 08/477,147 and 08/196,154. As set forth in §804 IB of the Manual of Patent Examining Procedure, the "provisional" double-patenting rejection will become an "actual" double-patenting rejection if either or

both of U.S. Serial No. 08/477,147 and 08/196,154 issues as a patent either prior to or on the same date as the present application. The effect of the terminal disclaimer would be to prevent the term of any patent issuing based on the present application from extending beyond the term of the patent based on U.S. Serial No. 08/477,147 and/or 08/196,154. The Examiner is respectfully requested to reconsider and withdraw the provisional double-patenting rejections of claims 100-126 over U.S. Serial No. 08/477,147 and 08/196,154.

Rejections Under 35 U.S.C. §103(a)

In ¶8 of the Office Action claims 100-112 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combined disclosure of six references, i.e., Wiegand et al (U.S. Patent 5,599,914) in view of Fiume et al (Critical Rev. Therapeutic Drug Carrier Systems, 4(4): 265-284, 1988), Ritter et al. (Seminars in Cancer Biology, 2:401-409, 1991), Kensil et al.(The Journal of Immunology, 146(2):431-437, (1991), and Marciani et al. (Vaccine, 9:89-96, 1991) and Uemura et al (J Biochem, 79(6):1253-1261, 1976).

In ¶9 of the Office Action claims 100, 112-115 and 117-126 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combined disclosure of eight references, namely Wiegand et al (U.S. Patent 5,599,914; issued Feb. 4, 1997; filed Nov. 24, 1989), Fiume et al (Critical Rev. Therapeutic Drug Carrier Systems, 4(4): 265-284, 1988) Livingston et al. (Cancer Research, 149:7045-7050, 1989) in view of Ritter et al. (Seminars in Cancer Biology, 2:401-409, 1991), Livingston et al. (U.S. Patent No. 5,102,663), Kensil et al.(The Journal of Immunology, 146(2):431-437, 1991), and Marciani et al. (Vaccine, 9:89-96, 1991) and Uemura et al (J Biochem, 79(6):1253-1261, 1976).

In ¶10 of the Office Action claims 95, 115 and 116 are rejected

under 35 U.S.C. 103(a) as being unpatentable over the same eight references discussed in the paragraph above in combination with Irie et al. (U.S. Patent No. 4,557,931).

It its respectfully noted that the nine references relied upon, in combination, to reject the claims under 35 U.S.C. §103(a) have been discussed in detail in, *inter alia*, applicants' Amendment In Response To August 27, 2002 Office Action filed March 17, 2003 wherein applicants described several features which they submit distinguish the invention. Those arguments are incorporated by reference therein and thus they will not be repeated here. Applicants have now, moreover, amended the claims such that, as discussed below they now recite several additional features which patentably distinguish the invention over the prior art.

The Inclusion Of The Adjuvant QS-21 Provides Unexpected Results That Demonstrate The Non-Obviousness Of The Invention

Composition claims 100 and 112 and method claims 114-115 were amended to specifically recite that the composition includes the adjuvant QS-21, i.e., a saponin derivable from the bark of a Quillaja saponaria Molina tree. During the December 2, 2003 interview, Applicants' representative directed the Examiner's attention to pages 94-95 of the application, which describe the unexpected results achieved with compositions as claimed including QS-21 as an adjuvant in comparison to those obtained with the use of corresponding compositions containing prior art adjuvants, i.e., BCG and DETOX.

Briefly, the specification teaches that local reactions to dosages of 100-200 µg of QS-21 were "quite different" (p.94, line 5) than those seen with comparable dosages of BCG and DETOX. It further states that the local response is more diffuse than the response generally seen with doses of DETOX or BCG inducing

comparable systemic symptoms (lines 8-11). It additionally teaches (lines 11-16) that a surprising feature of the subjects' response to QS-21 was that several days later (at most 10 days later) the local reactions had completely abated and there was no evidence that the vaccination had been administered to that site.

Applicants' specification additionally teaches (see paragraph bridging pps. 94-95) that QS-21, at any of the dosages used, resulted in a qualitatively different response than those achieved with the prior art adjuvants to GM2 ganglioside. The results obtained with QS-21 were contrasted with the immunogenic response achieved with the use of GM2-KLH vaccines alone or with optimal doses of BCG or DETOX, which were demonstrated to be substantially less effective than comparable compositions including QS-21. The specification additionally teaches that the results achieved by applicants demonstrate that the 100 and 200 µg doses of QS-21 induce the optimal antibody response against GM2 and that the 100 µg dose is better tolerated. These dosages are specifically recited in applicants' claims.

To summarize, applicants contend that the inclusion of the QS-21 in their claimed compositions produces two unexpected improvements over the results achieved with the prior art BCG and DETOX adjuvants: (1) the side effects attributed to such adjuvants are ameliorated with the use of QS-21; and (2) even at the lowest doses of the QS-21 adjuvant all of patients tested produced IgG antibodies against GM2. Applicants' independent claims, as amended, specifically recite the presence of the QS-21 adjuvant in an amount between about 10 µg and about 200 µg. Applicants contend that these recitations patentably distinguish the invention from the prior art.

During the December 2, 2003 interview the Examiner inquired

whether the results attributable to the inclusion of QS-21 were truly unexpected in light of the disclosure of the Kensil et al. reference. Applicants' representative pointed out that the reference does not suggest the use of QS-21 as an adjuvant and, in fact, teaches away from such use. For instance, page 435 of Kensil et al. makes clear that QS-7 adjuvant is more advantageous than QS-21 in that QS-7 is both less toxic and less hemolytic than QS-21. These advantages of QS-7 over QS-21 are important since the adjuvant is to be combined with the conjugate (discussed below) for administration to human subjects to stimulate or enhance the production of antibodies and/or to treat a human subject having cancer. Clearly, the increased toxicity and hemolytic activity of QS-21 disclosed in Kensil et al. teaches away from the use of QS-21 and toward the use of QS-7. In summary, Kensil et al. would not lead one of ordinary skill in this art to expect the surprising results achieved using QS-21 as the adjuvant, which results demonstrate the non-obviousness of applicants' claimed invention.

The Claimed Conjugate And the Molar Ratio Of Conjugated Ganglioside Derivative To Keyhole Limpet Hemocyanin Provide Additional Evidence Of Patentability

The claims recite, *inter alia,* (1) a conjugate of a GM2 or a GD2 ganglioside derivative and (2) a GM2 or GD2:Keyhole Limpet Hemocyanin molar ratio from 200:1 to 1400:1. These features further patentably distinguish the invention from the prior art cited to reject the claims.

The primary reference cited by the Examiner is U.S. Patent No. 5,599,914 to Wiegand et al. ("Wiegand"). Wiegand discloses at col. 7, lines 1-8 that ganglioside derivatives (GM3, GD3, GM2 and GM1) were reacted with Human Serum Albumin, i.e., not Keyhole Limpet Hemocyanin as recited in applicants' claims, and that the

HSA was derivatized with 16-18 SPDP molecules. The reference also teaches that this level was the preferred level (see, e.g., col. 7, lines 1-3). In contrast, applicants' claims recite a GM2 o GD2:Keyhole Limpet Hemocyanin molar ratio of between 200:1 and 1400:1. Such a ratio is neither taught nor suggested by Wiegand. The subject reference teaches away from the invention due to its teaching that the derivatization level of 16-18 is the "desired" level, and in view of the use of Human Serum Albumin as the carrier instead of Keyhole Limpet Hemocyanin as recited in applicants' claims. There is no disclosure in the reference, moreover, which would suggest the replacement of Human Serum Albumin with Keyhole Limpet Hemocyanin, or to produce a conjugate having a derivatization level different than that disclosed in Wiegand.

The Examiner combined Wiegand with Fiume et al. ("Fiume"), stating that "Wiegand in combination with Fiume teaches a glycoconjugate as claimed in claim 100 or 112." Applicants respectfully traverse this contention. The portion of Fiume cited by the Examiner (commencing at page 268) states that a **drawback** to the clinical use of the conjugates disclosed therein is their immunogenicity. The thrust is therefore to find a methodology for reducing the immunological effect of these conjugates. This teaching is opposite to that provided by the applicants about their present invention in that the purpose of the conjugates of the present invention is to increase, **not** to reduce, the immunogenic effect (see, for example, claim 114).

Fiume not only teaches away from the present invention, it contains no disclosure which would suggest its combination with Wiegand. Wiegand discloses the formation of a composition for use in producing an immunogenic response. In contrast, Fiume teaches to proceed in a diametrically opposed direction, i.e., to seek

compounds having a reduced immunogenic effect. These contrasting teachings would lead a skilled artisan away from combining Wiegand with Fiume. Further, even if combined, such combination would not produce the claimed glycoconjugate.

The Improved Results Obtained With Applicants' Compositions Evidence The Patentability Of These Compositions

Applicants provided a reference by Chapman et al., Clinical Cancer Research, Vol. 6, pp. 874-879 (March 2000) entitled, "Induction of Antibodies Against GM2 Ganglioside By Immunizing Melanoma Patients Using GM2-Keyhole Limpet Hemocyanin + QS21 Vaccine: A Dose-Response Study" (hereinafter "Chapman") as Exhibit E to their Amendment filed April 3, 2002. Another copy of this reference is provided as **Exhibit D** herewith.

As noted at page 26 of applicants' April 3, 2002 response, in clinical trials melanoma patients vaccinated with GM2-KLH + QS-21 (i.e., the claimed composition) made using the conjugation procedure described in the present application, produced high titer IgM and IgG antibodies specific for GM2. These clinical results led the authors (including Dr. Philip O. Livingston, a co-inventor of the present invention) to state that the GM2-KLH/QS-21 composition, formulated as presently claimed, "is more immunogenic than our previous formulation." (see Abstract). The "previous formulation" comprised GM2 and *bacilli Calmette-Guerin* (BCG).

The Livingston paper and the Livingston '663 U.S. Patent both disclose the GM2-BCG formulation, i.e., the "previous formulation". The improved formulation described in the present application and claimed herein is distinguishable thereover in that the "previous formulation" does not comprise the same components as the compositions recited in applicants' claims.

Further, not only are applicants' formulations made with different components, the present claims additionally recite specific ranges for the components included in these formulations. As demonstrated in Chapman, the presently claimed compositions produce significantly improved results in contrast to those achieved with the previous formulations.

In summary, the claimed compositions are distinguishable over those disclosed in the Livingston references as, due to (1) differences in the components from which they are formed, and (2) the relative amounts of the conjugate and the saponin in the claimed compositions, as taught by Chapman they produce a substantially improved immune response to subjects in a clinical setting.

The remaining references cited by the Examiner, i.e., Ritter et al., Marciani et al., Uemura et al. and Irie et al., do not remedy the deficiencies of the references discussed above. Applicants submit that the claimed invention is patentably distinguishable over all of the cited references and respectfully request the Examiner to reconsider and withdraw the rejections of the claims under 35 U.S.C. §103(a).

NEW GROUNDS OF REJECTION

In ¶12 on page 11 of the Office Action claim 95 is objected to as depending from a canceled claim (claim 94). Claim 95 has been cancelled and thus the objection to that claim is moot.

In ¶13 on page 11 of the Office Action claims 103-105 and 126 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

The Examiner stated that claims 103-105 recite ranges that are not

described in the specification. Claims 103-105 have been cancelled in this Amendment and thus the §112 rejection of those claims is moot.

The Examiner additionally stated that claim 126 is drawn to a method for delaying recurrence of melanoma. The Examiner stated that there does not appear to be support in the specification for methods for delaying recurrence of melanoma. The Examiner stated that the passages pointed to by applicant as providing support do not teach the recited references and do not teach methods for delaying the recurrence of melanoma. In response, claim 126 has been cancelled and thus the rejection of claim 126 under §112 is also moot.

SUMMARY

For the reasons set forth, applicants respectfully request that the Examiner reconsider and withdraw the various grounds of objection and rejection and earnestly solicit allowance of the now pending claims.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' attorneys invite the Examiner to telephone either of them at the number provided below.

A check for FIVE HUNDRED AND THIRTY DOLLARS ($530.00) is enclosed herewith. This amount had been determined by adding the fee of $475.00 due for the three-month extension of time to the fee of $55.00 due under for the filing of the Terminal Disclaimer ($475.00 + $55.00 = $530.00). If any additional fees are required, authorization is hereby given to charge the amount of such required fee(s) to Deposit Account No. 03-3125.

Respectfully submitted,

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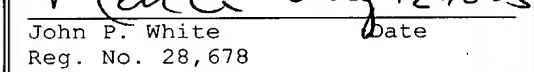
I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450



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